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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/487,550	06/07/95	ANDERSON	

EXAMINER: [illegible]

ART UNIT	PAPER NUMBER
GAMBEL, P	8

18M1/0107

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DATE MAILED: 1806
01/07/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-20 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-20 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

DETAILED ACTION

1.The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

2. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).

3. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

For example, the use of the trademark "SEPHAROSE" has been noted in this application. It should be capitalized or accompanied by the ™ or ® symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The specification is objected to and claims 15-20 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

A) In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs can be species- and model-dependent, it is not clear that reliance on the in vitro experimental observations accurately reflects the relative efficacy of the claimed therapeutic methods and pharmaceutical compositions applying primatized B7-specific antibodies encompassed by the claimed invention. For example, applicant disclosed primatized antibodies 16C10, 7C10, 20C9 and 7B6 display varying degrees of inhibitory activity and apparently at 50% inhibitory levels only where the antibody was added at the onset of proliferative in vitro assays.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Kahan clearly states that no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Cur. Opin. Immunol., 1992; see entire document, particularly page 558, column 2).

Ward et al. addresses the issues associated with selection of interventions of adhesion molecules as an approach to anti-inflammatory therapy (Therapeutic Immunol., 1994). At the current time of the article (1994), in humans there are relatively few conditions in which there is clear-cut evidence of the presence and participation of given adhesion molecules in humans (page 166, column 1, paragraph 1). Also, monoclonal antibodies are not likely to be the ultimate approach for in vivo blocking of adhesion molecules, even though they will likely provide important information (see pages 167-170, particularly Concluding Remarks).

It is noted that animal models validate concepts based on studies of human disease, however, such studies are limited to the acute as opposed to chronic nature of the disease. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. For example, experimental protocol usually rely upon the antibody antagonist is administered at the same time of the inflammatory stimulus or onset . It is known that Immunosuppression is much easier to achieve under such controlled conditions to defined antigens in mice than that experienced in the human immunoregulatory diseases targeted by the claimed invention, including chronic diseases such as autoimmune diseases and GVHD.

Although the B7:CTLA-4/CD28 pathway is important in immune responses, including T cell responses. The instant methods encompass the use of either B7-specific or CD28-specific antibodies alone in therapeutic methods. Guinan et al. (Blood, 1994) reviews the pivotal role of such pathways in transplantation tolerance and tumor immunity and indicates that there are multiple B7 species with distinctive structures and functions; indicates that blocking via CD28 or via B7 specificities can partially inhibit T cell responses but that each agent is limited in said inhibition when compared to the use of multiple specificities or CTLA-4; and that T cells respond normally after withdrawing T cells from inhibitory conditions (see entire document).

In addition, Lenschow et al. (Transplantation, 1995) disclose that the use of anti-B7-1/anti-B7-2 antibodies can suppress T cell responses in vitro but that such antibodies in isolation were limited in their ability to inhibit T cell responses in vivo.

Also, Perrin et al. (J. Neuroimmunology, 1996) disclose that there are distinct roles for CD80 (B7-1 and CD86 (B7-2) in an autoimmune model; that anti-CD80 antibodies were only effective in first disease episodes; and that anti-CD86 antibodies were not effective.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based and antibody-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods using primatized B7-specific antibodies alone are effective for inhibiting T cell responses.

B) Applicant claims read on antibodies have a single specificity (e.g. B7.1 or B7.2), have a cross-reactive specificity (B7.1 and B7.2 specificity) or have a bi-functional specificity (B7.1 and B7.2). However, there is insufficient information or enablement for the support for antibodies primatized antibodies having the following properties; a cross-reactive specificity (B7.1 and B7.2 specificity) or have a bi-functional specificity (B7.1 and B7.2).

6. Applicant is invited to clarify whether reliance on the NEOSPLA exression vector system and the primatization protocols disclosed in copending 08/379,072 and 08/149,099 are required for the enablement of the instant compounds, compositions and methods that require primatized B7.1/B7.2-specific antibodies. If so, applicant is reminded of the following.

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See *In re Fouche*, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

7. The specification is objected to and claims 2-11 and 14-20 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

It unclear if a cell line which produces an antibody having the exact structural and chemical identity of 16C10, 7C10, 20C9 and 7B6 are known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species 16C10, 7C10, 20C9 and 7B6. Deposit of the appropriate hybridomas would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

It is noted that if the claimed amino acid sequences or nucleic acid sequences set forth in claims 6-11 and 14 encode the entire primatized B7.1-/B7.2-specific antibodies, then a deposit for said antibodies is not required. The sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin. Note that satisfaction for the biological deposit of the specific 16C10, 7C10, 20C9 and 7B6 antibodies require the disclosure and recitation of their entire amino acid sequence and not based upon partial sequences.

It is noted that "has the sequence" and having the sequence" are considered closed language phrases, the same as "consisting of".

8. Claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-20 are ambiguous in the recitation of claim 1 wherein it is unclear whether the antibodies have a single specificity (e.g. B7.1 or B7.2), have a cross-reactive specificity (B7.1 and B7.2 specificity) or have a bi-functional specificity (B7.1 and B7.2).

B) Claims 3 and 4 are indefinite in the recitation of "depleting antibody" and "non-depleting antibody" because it is not clear which specific activity or to what degree is intended.

C) Claims 2-11 and 14-20 are indefinite in the recitation of "16C10, 7C10, 20C9 and 7B6" because their characteristics are not known. The use of "16C10, 7C10, 20C9 and 7B6" monoclonal antibodies as the sole means of identifying the claimed antibodies renders the claim indefinite because thee terms are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct cell lines or hybridomas.

D) Claims 6-11 and 14-20 lack clarity in that do not recite the particular SEQ ID NOS. intended by amino acid and nucleic acid sequences.

E) Claims 16-17 are indefinite and ambiguous in the recitation of "treating a disease" since no disease or therapeutic endpoint is recited.

F) It is noted that the use of the protein designations "human B7.1" and "human B7.2" antigen refer to those particular molecules disclosed on pages 9-11 of the instant specification

Alternatively, claims 1-20 are indefinite in that they only describe the compositions of interest by an arbitrary protein name,"human B7.1" and "human B7.2". While these names may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein and variants thereof. Others in the field may isolate the same protein and give such an entirely different name. Applicant should particularly point out and distinctly claim the "human B7.1" and "human B7.2" antigens by claiming characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of.

G) The amendments must be supported by the specification so as not to add any new matter.

9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

10. Claims 1-20 are rejected under 35 U.S.C. § 103 as being unpatentable over Linsley et al. (Ann. Rev. Immunol., 1993) or Linsley et al. (U.S. Patent No. 5,434,131) or Linsley et al. (U.S. Patent No. 5,521,288) in view of Cohen (Science, 1993), Hathcock et al. (Science, 1993), Freeman et al. (Science, 1993)Freeman et al., (Science, 1993) and art-known procedures and motivation to primatized antibodies for diagnostic and therapeutic regimens as acknowledged on pages 14-16 and 21-27of the specification (e.g. Newman et al. Biotechnology, 1992). The instant claims are drawn to primatized B7.1-/B7.2-specific antibodies, transfectomas expressing said antibodies and their use in inhibiting T cell-mediated pathology.

Linsley et al. (Ann. Rev. Immunol., 1993) or Linsley et al. (U.S. Patent No. 5,434,131) or Linsley et al. (U.S. Patent No. 5,521,288) all teach the important role of CD28:B7 interactions in regulating immune responses, inhibiting said immune responses encompassing transplantation and autoimmunity with B7-specific antibodies. These references differ from the claimed inventions by not explicitly reciting B7.1 and B7.2 specificities and not teaching their primitization.

Cohen (Science, 1993), Hathcock et al. (Science, 1993), Freeman et al. (Science, 1993)Freeman et al., (Science, 1993) all teach the structure and function and therefore the contribution of B7.1 and B7.2 specificities to regulating the immune responses as well as targeting either and both specificities as therapeutic regimens associated with immuonoregulatory disorders encompassed by the claimed methods.
These combined references clearly teach that the combination of targeting B7.1 and B7.2 had greater potential in downregulating the immune response than either alone.

In agreement with the specification, it was well known in the art at the time the invention was made to primatized/humanized antibodies to have readily available reagents suitable for human diagnosis and therapy and their respective use in primate models. For example, Newman et al. teach the protocols of primatizing antibodies including the use of computer analysis of the instant invention (see entire document). Transfectomas were convenient means of providing a ready source of homogeneous antibodies of interest. Although the references are silent about the exact sequences of the claimed B7.1-/B7.2-specific-specific antibodies, the recombinant techniques and computer analyses of immunoglobulin sequences as taught by the references would have resulted in the same or very

nearly the same characteristics of the instant claims since both the references and instant invention use the same techniques, the same antibody specificities and the same goals. The generation of various forms of said antibodies would have resulted in both depleting and non-depleting antibodies, each with its own suitability based upon the needs of the targeted patient population or diagnostic assay. The ordinary artisan would have achieved either the same or functional equivalents of the instant 16C10, 7C10, 20C9 and 7B6 B7.1-/B7.2-specific antibodies.

One of ordinary skill in the art at the time the invention was made would have been motivated to select B7.1-specific, B7.2-specific antibodies and bispecific antibodies thereof as diagnostic and therapeutic agents in treating human immunoregulatory disorders encompassed by transplantation and autoimmunity. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. No claim is allowed.

12. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242 or (703) 305-7939.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
January 6, 1997